REMARKS

Claims 1-11, 13-14, 17-18, 21, 24, and 26-27 are currently under consideration. In the Advisory Action dated March 10, 2009, the Examiner indicated that the rejection of the claims under 35 U.S.C. § 102, second paragraph had been withdrawn. Additionally, the Examiner indicated that Exhibits C-E had not been received. Submitted herewith are copies of Exhibits C and D, originally filed on February 19, 2009. Regarding Exhibit E, Applicant has attempted to obtain a copy of Exhibit E through public databases but has not yet been successful. Applicant is currently attempting other means for obtaining a copy of Exhibit E and will provide a copy once it has been received.

1. The Claims Are Not Obvious in View of Minden and Nelson

The rejection of claims 1-11,13-14,17-18, 21, and 24-27 is maintained under 35 U.S.C. §103(a) as being unpatentable over Minden et al. WO 02/086081 A2 ("Minden") and Nelson et al. U.S. Patent 6,887,713 ("Nelson").

According to the Examiner, Minden teaches methods of identifying a protein via assigning (i.e. separating) binding reagents to designated locations on an array, detecting the binding patterns, and comparing the binding pattern to a reference set (i.e. characterizing; please refer to the abstract, paragraphs [0005-0012], [0028-0032], [0035-0044], [0072-0074], [0077], [00117], Figures 1-11, and Table 1). In addition, Minden is said to further teach (i) that the molecular weight or mass of the binding reagents can be determined and that spectrometry can be utilized; (ii) that more than one protein can have the same epitope thus the common epitopes (i.e. more than one) would bind to the same defined location; (iii) that the total protein content of a cell or tissue can be utilized as the protein mixture; (iv) that the protein mixture can be fragmented with various chemical or enzymatic methods including trypsin; (v) that trypsin cleavage forms a peptide or epitope (i.e. motif) with C-terminal lysine or arginine residues; (vi)

that the peptides or epitopes (i.e. motifs) can be at least three amino acids in length and can have at least two variable amino acids; (vii) that arrays can have different binding molecules at spatially addressable locations which bind to different binding reagents; (viii) that the protein mixture may comprise all (i.e. at least 10% of the peptides) of the proteins and that the epitopes cover the binding mixture; (ix) that the array can have 2-100 different proteins; (x) that the binding reagents can be antibodies; (xi) that the proteins are compared to a reference set (i.e. characterizing; (xii) that the reference set can include prediction about binding based on the predicted digests of a protein mixture; (xiii) that various binding reagents can be compared to a reference set or to other binding reagents.

According to the Examiner, although Minden does not specifically teach determining the abundance of the proteins by the use of desorption mass spectrometry or collision induced dissociation mass spectrometry, for present claims 1, 24, and 26, Nelson teaches analyzing complex biological mixtures utilizing "lab-on-a-chip" (i.e. chip-based microarrays) and MALDI-TOF (i.e. combination of both desorption mass spectrometry and collision induced dissociation mass spectrometry) wherein the proteins are quantified (i.e. abundance), internal reference standards are utilized, and determining the amount (i.e. abundance) of the proteins. According to the Examiner, the claims would have been obvious because the substitution of one known element (i.e. mass spectrometry providing mass information only) for another (i.e. mass spectrometry providing both mass and abundance information; MALDI-TOF) would have yielded predictable results to one of ordinary skill in the art at the time of the invention and/or (b) the claim would have been obvious because a particular known technique (i.e. MALDI-TOF utilized to determine mass and abundance of proteins) was recognized as part of the ordinary capabilities of one skilled in the art. See *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007).

Applicant maintains that, for reasons detailed below, the present invention is not render obvious by Minden or Nelson, either alone or in combination.

In the Advisory Action dated March 10, 2009, the Examiner indicated that Applicant's previous arguments distinguished the present invention as being directed to a "mixture," however, the Examiner notes that this feature is not a limitation of the claims. The Examiner also noted that previous arguments have related to the feature of no previous knowledge of the composition of the sample, without this feature being included in the claims. In response, Applicant has amended Claim 1 to specify (i) that the heterogenous sample is a "mixture" of proteins, peptides, protein fragments or peptide fragments and (ii) that the "composition of the heterogenous sample is unknown prior to conducting the method."

As previously argued, Applicant maintains that the current invention is directed to a method that is capable of separating and characterising protein/peptide mixtures of unknown composition, for example as extracted from a cell or tissue sample composition of such crude proteomes (e.g. cell and tissue extracts), and throughout the application, it is demonstrated that the invention can be used to target such heterogeneous sample formats for which advanced knowledge of their composition is not a pre-requisite. For example, this is demonstrated in paragraphs [0010], [0100], [0107], [0109] and [0167-0170] of the specification. In particular, paragraphs [0167-0170] show utilization of the method in analysis of a crude digested mouse liver homogenate. This sample represents a heterogeneous sample mixture of unknown composition.

In contrast to the present invention, Minden describes work with compositions having a known (or substantially known) composition. Nelson describes the analysis of a complex biological mixture in a chip based microarray coupled with MALDI-TOF protein analysis tools. Thus, Nelson merely provides a disclosure of an alternative measurement tool to those of

Minden. Even when the disclosure of Minden and Nelson are combined ***they do not disclose the analysis of mixtures of heterogeneous proteins/peptides where the mixture is of unknown composition***. Instead, Minden and Nelson combined describe the analysis of protein samples of substantially known composition. The analysis yields information on the mass and abundance of proteins in the sample.

Clearly, this differs from the presently claimed invention. Furthermore, there is no suggestion in either Minden or Nelson that the method of Minden could be applied to samples of unknown composition. In particular, the purpose of the method of Minden (irrespective of the analysis tool used) is to select (or eliminate) specific binders. This is a completely different concept to the claimed invention which is directed to the analysis of the composition of complex protein-based samples of unknown constituents.

For the sake of argument, the following scenerio is provided to demonstrate what would happen if the approach of Minden was adopted in the method of the presently claimed invention. An array would be fabricated by dispensing the complex sample into discrete positions on the array. Subsequently, the array would be subjected to binder molecules and unbound binders would be washed away, after which any specifically bound binders would be detected/identified. This set-up is known by those of skill in the art as a reversed binder-array (e.g. reversed antibody array) (or protein array in common terms). The Examiner has indicated that this set-up would give equal results compared to the claimed invention, i.e. that they are inter-changeable.
In the claimed invention the array set-up, known by those of skill in the art as a binder array (e.g. antibody array), would be fabricated by dispensing the binders into discrete positions on the array. Next, the array would be subjected to the complex sample and unbound sample as washed away, whereafter any specifically bound protein(s) or peptide(s) are detected/identified.

For reasons detailed below, Applicant respectfully submits that the belief that these conceptually different set-ups by necessity would give equal results is incorrect.

Firstly, it is known by those of skill in the art that a protein or peptide can adopt different conformations depending on whether the protein or peptide is in solution or absorbed onto a solid support (and allowed to dry out, which is common consequence in most array fabrication steps). If the protein or peptide adopts different conformations the reactivity of the binder molecule in turn would be affected/impaired, thereby generating set-up dependent binding patterns as the out-put results. Hence, different results would be generated depending on whether binder arrays or reversed binder arrays were used. This scenario is schematically outlined in attached Exhibit A (Figure 1A).

Furthermore, support for the contention that conformation changes can occur between proteins or peptides in solution or absorbed onto a solid support can be found in the following attached Exhibits: Feng (2007; Exhibit B), Buijs (1996; Exhibit C), Kondo (1992; Exhibit D) which all show conformational changes occur; Norde (2000; Exhibit E) which shows denaturation can be the result of contacting a surface; Hlady (1996; Exhibit F) which is a review describing possibly detrimental effects of the events during protein adsorption to solid surfaces; and Manjon (1983; Exhibit G) and Mannen (2001; Exhibit H) and Peng (2003; Exhibit I) which all demonstrate that conformational changes can occur on immobilisation.

Secondly, and most importantly, the reversed binder array approach, of Minden, is completely incompatible with the concept of the claimed invention due to the nature of our Applicant's molecules. If the set-up by Minden was adopted, the complex sample would be arranged into discrete positions on the array. Each unique spot would then contain all the different proteins or peptides present in the samples. Many different proteins or peptides sharing the same motif (or different motifs) as specified in the invention would then potentially be

present in each discrete spot. Binder molecule would then be added and unbound binders washed away before the final read-out based on detecting any bound binder molecules was performed.

In the claimed invention, binder molecules are used specifically for a motif shared between several different proteins and peptides. By simply detecting a bound binder molecule as in Minden, it would only be possible to tell that the binder has bound, and not anything about the identity of the protein(s) or peptide(s) that the binder had bound to. This could represent anything from a single protein or peptide up to numerous different proteins or peptides. Thus, even if Minden was followed and combined with the set-up by Nelson, the MALDI-TOF mass spectrometry only provides the mass and potentially sequence (and identity) of the binder molecule. This would give detailed information about the motif specific binder molecule itself that bound to this spot, but it would not provide any information regarding the identity of the motif –carrying protein(s) or peptide(s) present in the spot to which it had bound to. This scenario is schematically outlined in attached Exhibit A (Figure 1B).

Thus, the combined teachings of Minden and Nelson are conceptually different and not interchangeable with the claimed invention and would give strikingly different end results. Hence, the claims are non-obvious over the combination of Minden and Nelson and, therefore, the rejection under 35 U.S.C. §103 should be withdrawn.

2. The Claims Are Not Obvious in View of Minden and Barry

The rejection of claims 1-11, 13-14, 17-18, 21, 24, and 26-27 is maintained by the Examiner under 35 U.S.C.§ 103(a) as being unpatentable over Minden and Barry et al. WO 0225287 ("Barry"). Barry is said by the Examiner, to teach methods of determining the binding and mass of trypsin digested proteins including antibodies from a cell including phage or tissue

sample immobilized on an array. According to the Examiner, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of identifying proteins taught by Minden with the MALDI-TOF analysis taught by Barry.

Applicant maintains that, for reasons detailed below, the present invention is not render obvious by Minden or Barry, either alone or in combination.

First, in light of the amendments to claim 1 to specify (i) that the heterogenous sample is a "mixture" of proteins, peptides, protein fragments or peptide fragments and (ii) that the "composition of the heterogenous sample is unknown prior to conducting the method" the rejection based on Minden and Barry is no longer appropriate.

Furthermore, the arguments presented above regarding the rejections of the claims based on Minden and Nelson also apply to the rejections based on Barry and Nelson, the only difference being that Barry is a different reference describing MALDI-TOF mass spectrometry. Accordingly, the claims are non-obvious over a combination of Minden and Barry.

In light of these remarks, Applicant respectfully requests that the obviousness rejections be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is believed that the subject claims are in condition for allowance, which action is earnestly solicited. If, in the opinion of the

Examiner, a telephone conference would expedite prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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